January 31, 2026

Dear Friends,

I hope the new year has started well for you and your family. Thank you, as always, for being part of the Wolfram syndrome community. Your trust, patience, and partnership mean a great deal to us. Everything we do in the clinic, the clinical trial unit, and the laboratory is driven by a single purpose: to improve the lives of individuals and families living with Wolfram syndrome. Our shared goal is CURE4WOLFRAM, and every visit, study, and experiment moves us one step closer. I would like to share where we are now, what we are learning, and how these efforts are coming together as we move into 2026.

New Drugs and Supplements

We are actively developing a systematic platform to identify medications and supplements that may benefit individuals with Wolfram syndrome. Using patient derived induced pluripotent stem cells, we generate brain cells in the laboratory that closely reflect the biology of Wolfram syndrome. These cells allow us to directly test existing drugs, supplements, and new compounds to see whether they improve cell survival, reduce stress responses, support mitochondrial function, or restore healthier cellular balance. Our highest priorities include antioxidants, sigma 1 receptor agonists, NAD activators, idebenone, GLP-1 receptor agonists, and other compounds that target endoplasmic reticulum stress and mitochondrial dysfunction. We also have a long list of additional candidates based on scientific rationale and emerging evidence. This platform allows us to evaluate potential therapies before moving toward clinical studies. We plan to expand this effort and will continue to share updates as we learn more.

AMX0035 Clinical Trial: Where We Are Now

Our Phase 2 clinical trial of AMX0035, conducted in close partnership with Amylyx Pharmaceuticals, continues to move forward. In May 2025, long term 48-week data were announced. In several participants, we observed signs of sustained improvement in pancreatic beta cell function and blood glucose control. Vision measures appeared stable and, in some cases, showed modest improvement. Importantly, the treatment has continued to demonstrate a favorable safety profile. These findings are encouraging, and careful interpretation and continued study remain essential. We have shared these results at scientific meetings, and our manuscript reporting the entire results is currently being revised following constructive feedback from peer reviewers. We are working diligently toward final publication. We know many families are eager to hear about next steps. Advancing to the next phase of a clinical trial requires well-designed outcome measure assessment plans. Please know that we are working closely with Amylyx and doing everything we can to move this process forward as quickly as possible.

Gene Editing Therapy: Addressing the Root Cause of Wolfram Syndrome

Over the past several months, we have made particularly strong progress in gene-editing therapy development. Because Wolfram syndrome is caused by pathogenic changes in the WFS1 gene, correcting these changes has the potential, in theory, to address multiple aspects of the disease. Using patient derived induced pluripotent stem cells, which can be differentiated into any cell types, we have successfully corrected WFS1 pathogenic changes in laboratory generated brain cells in the tissue culture dish. After correction, these cells show improved survival, healthier energy production, reduced oxidative stress, and more stable calcium balance. We are seeing similar encouraging improvements in insulin-producing pancreatic cells derived from patient iPSCs.

At the same time, we are working intensively on one of the most important challenges in gene editing: safe and effective delivery. For gene editing to work, we need to deliver both an enzyme and a small piece of DNA

efficiently and safely to the affected organs. Our current efforts are focused on developing new delivery systems for the brain and the eye. Rather than relying on conventional approaches such as AAV or peptides, we are investing significant effort in nanoparticles and engineered virus-like particles, which we believe offer a safer and more adaptable path forward. Our goal is to build a strong foundation using patient-derived cells and humanized mouse models, and to use these data to lay the groundwork for a future clinical trial.

Regenerative Therapy and Neuroprotection

In parallel, we continue to develop regenerative therapies aimed at protecting vision and brain function. One of our main efforts centers on a naturally occurring neurotrophic factor called MANF, a molecule that helps cells survive and recover when they are under stress. MANF is particularly relevant to Wolfram syndrome because it supports pathways that help cells cope with endoplasmic reticulum stress, which is a key contributor to vision loss and neurodegeneration in Wolfram syndrome. Because of funding constraints, we had to pause this work for a period of time. Thanks to recent generous support, the project has regained momentum, and we are now steadily generating new data. We look forward to sharing our progress at the next Wolfram syndrome conference.

Building Better Care Through International Clinical Guidelines

One of the most consistent messages we hear from families and healthcare providers is the need for clearer, evidence-based guidance for Wolfram syndrome care. To meet this need, we have been developing international consensus clinical guidelines for Wolfram syndrome. This effort has been supported by the Snow Foundation and Wolfram Syndrome UK, both of whom serve as core committee members. Our team has carefully reviewed more than 350 scientific publications and drafted recommendations across many areas of care, including genetics, endocrinology, ophthalmology, neurology, urology, gastroenterology, psychiatry, and the transition from pediatric to adult care. Nearly 50 experts from around the world have already shared their insights and expertise. We are now refining these recommendations using the Delphi method, a structured process designed to build expert consensus. In each round, feedback from experts is reviewed, incorporated, and reassessed until broad agreement is reached among experts. This work takes time and careful attention. With each round, the guidelines become clearer and more practical for day-to-day patient care. We are steadily moving toward completion, with the goal of providing guidance that reflects both the best available science and real-world clinical experience.

Wolfram Syndrome and Related Disorders Clinic

Our multidisciplinary clinic at Washington University Medical Center in St. Louis remains committed to providing comprehensive and coordinated care for patients with Wolfram syndrome and WFS1-related disorders. We continue to prioritize one-day or two-day visits whenever possible for families traveling long distances, including out-of-state and international families. Our nurse navigator for Wolfram syndrome patients, Ashley Raterman, coordinates these efforts and serves as a key point of contact for families.

More information is available at
https://wolframsyndrome.wustl.edu/
Email: WolframSyndrome@wustl.edu

With Gratitude and Determination

Thank you for your continued support and encouragement. Your trust and resilience mean a great deal to our entire team. I remain deeply committed to this work, and my team and I are working very, very hard every day,

guided by the belief that therapeutic development plans shaped by patients and families can lead our ultimate goal, CURE4WOLFRAM.

With gratitude and hope,
Fumi

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